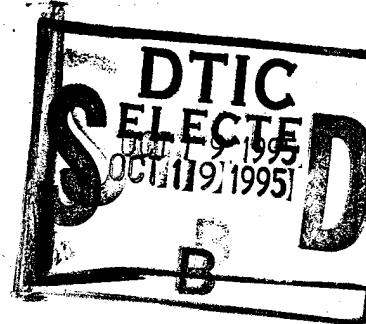


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*Beth Mueller* 9/15/95  
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## I. INTRODUCTION

### *A. Nature of the problem*

The incidence of breast cancer among women less than 45 is increasing, and young women appear to have relatively poor survival. The prognosis may be even worse for women who are pregnant at diagnosis however, the effect on survival is unknown. As the increase in breast cancer incidence among younger women coincides with a trend towards delayed childbearing, information regarding the association of subsequent pregnancy and survival is needed so that women with breast cancer and their physicians can make informed choices concerning family planning.

At present there is no general consensus among physicians providing care to young women with breast cancer about how to advise them regarding their future reproduction (14), and the lay press clearly demonstrates that this is an issue of concern to those women affected. Current clinical recommendations concerning a waiting period of 2-3 years (the peak period of recurrence) after the conclusion of breast cancer treatment before attempting pregnancy are based on psychosocial and moral issues rather than scientific studies linking pregnancy with poorer survival(3,14). Women who survive their initial breast cancer treatment are justifiably confused concerning their future.

### *B. Previous work*

The effect on survival of a pregnancy conceived after breast cancer treatment has been little studied and the available results have only incompletely accounted for confounding and selection bias. There are several reasons why few studies have evaluated the effect of subsequent childbearing on survival among women with breast cancer. First, although breast cancer is one of the most common of female cancers, young women in their childbearing years account for a relatively small percent of all primary cases (1). Second, only a minority of them will go on to conceive and carry a pregnancy to term afterwards(2). Thus it is difficult to identify and study a large enough number of women to obtain valid results.

Survival may be relatively worse for women who are pregnant at the time of their primary diagnosis of breast cancer, although it is difficult to generalize from previous studies because of varying definitions and populations used. Studies of pregnancy-associated breast cancer may not distinguish between women diagnosed during pregnancy soon after pregnancy, during lactation, or even subsequent to treatment. Most studies have included women who have undergone mastectomy only, and the time periods covered have encompassed wide variation and changes in clinical treatment. Details of treatment, which are likely to have an impact on survival, are rarely considered in the analysis (3). Early reports suggested that breast cancer diagnosed during pregnancy was associated with poor survival (3,4), however, this observation may be confined to node-positive breast cancer diagnosed during gestation. Recent studies that have controlled for the effects of age and stage at diagnosis however, have conflicting

results. Peters (5), observed no difference in stage between women diagnosed during pregnancy or lactation and a control series matched on age and stage of disease. These results have been supported by at least one other study (6). which also suggested that young age (less than 40 years), rather than pregnancy itself may be the negative prognostic factor responsible for previous studies suggesting poor survival in pregnant women, as young women in their study had a relatively higher proportion of aggressive estrogen receptor-negative tumors than older women. Petrek et al. (7) followed up 56 pregnant women treated surgically at a single facility, and a similar group of 166 non-pregnant patients, and reported similar 5 year survival (82%) among node-negative women who were pregnant and nonpregnant. Node-positive women who were pregnant, however, had slightly worse 5 year survival (47%) than node-positive nonpregnant women (59%). Two other recent studies that controlled for age and disease stage, however, suggest a significantly worse survival among women diagnosed during pregnancy (8-9). There have been several reasonable biological rationales suggested to support an association of pregnancy-associated breast cancer with poorer survival, including variations in hormone levels and immunologic changes such as a decrease in cell-mediated immunity during pregnancy (3,12). Uncovering the true association is further complicated, however, as the elapsed time from detection to diagnosis is frequently longer in pregnant women than non-pregnant women, which may account, to some extent, for a relatively poorer survival (3,12).

An early study (1937) reported that women with pregnancies after surgery had better survival than those whose breast cancer was diagnosed during pregnancy or lactation(4). Several subsequent studies that have compared women with pregnancies after breast cancer diagnosis to comparison groups without pregnancies suggest no difference in survival. Peters(5) reported 72% vs. 50% 5 year survival in patients with and without subsequent pregnancy, even after controlling for age and stage at diagnosis. When only patients who became pregnant within 6 months of surgery were included, however the proportion of women with subsequent pregnancies surviving at 5 years dropped to 54% indicating the need to control for bias due to the decreased likelihood of pregnancy among women with more rapid disease progression. One study matched 32 patients with pregnancies to two controls (on the basis of clinical stage, node involvement, age, and initial survival after surgery) and concluded that pregnancy did not adversely affect survival (10). However, they only followed patients for 5 years after diagnosis and did not include patients with other treatment modalities. Another study followed up radical mastectomy cases without chemotherapy from 1930-1975 at one facility (47 with pregnancies/960 without pregnancies) and reported no differences in 5 year survival. Among node-negative cases, 5 year survival was 77% for women with pregnancies vs. 70% for those without; among node-positive cases, it was 56% vs. 53% (11). The authors conclude that pregnancy after treatment of breast cancer has no effect upon prognosis, however, their study included only women with radical mastectomies treated at a single facility and could not address pregnancy and survival after other treatments.

A recent Swedish study (1995) compared women diagnosed with breast cancer without pregnancies to women with breast cancers and either prior (N=173) or subsequent pregnancies (N=50) within 5 years of diagnosis. This study compared all incidences of primary operable breast cancer diagnosed in the area of Stockholm between 1971 and 1988. The authors studied tumor size, ER status, age, and found results that supported Petrek's earlier conclusion that pregnancy had no adverse effect on the prognosis of breast cancer (13). They also concluded that a subsequent pregnancy may be related to a decreased risk of distant dissemination. (relative hazard = 0.48,  $p=.14$ ). An examination of this with a greater number of subjects, longer follow-up, and with an examination of treatment modalities such as we are conducting, needs to occur.

### ***C. Purpose of present work***

The purpose of the present study is to obtain data from a large enough sample size, and with a diverse enough population, in order to evaluate the relative survival of women with and without births among young women with breast cancer. By obtaining data from three population-based cancer registries (Seattle, Los Angeles, and Detroit) we can identify all women <45 years, with breast cancer. Similar clinical information is obtained from all registries, thus it will be possible to evaluate the effects of stage, node status, and other important factors on survival. Using birth certificate data from all three states (Washington, California, and Michigan) we will ascertain those with and without births in order to form the exposed and comparison groups. Additional data obtained from previous case-control studies conducted in Los Angeles and Seattle will allow subanalyses with information related to family history, body mass, estrogen/oral contraceptive exposures and other data that may potentially influence the relationship of interest. In addition, the use of data from three such ethnically diverse areas will allow us to further examine this relationship in a way that it has not been done before.

### ***D. Methods of approach***

Our study makes use of three population based cancer registries and birth certificate records in their respective states in order to determine the subsequent childbearing experience of young women with primary breast cancer. Women <45 years of age at diagnosis of breast cancer have been identified in the Seattle area, Detroit, and Los Angeles cancer registries. Data tapes containing birth certificate information from 1980-1994 from all three states will be merged with cancer registry information to identify women with subsequent births. As all registries routinely link to death certificate information, it will be possible to screen subjects for survival.

After linkage of registry data to birth certificates and identification of women with births, a comparison group of women without births will be identified. They will be drawn from among women <45 years of age with breast cancer who were found not to have had births and will be linked on the basis of relevant characteristics (age, race, stage



of disease at diagnosis, year of diagnosis) and will be selected to consist of only those who have survived up until the reference date (date of pregnancy for women with births) of their respective match. This latter step will be done to ensure the relative health of both the exposed (those with births) and comparison groups. Both groups will be similarly followed up for survival and disease recurrence using routine methods at the cancer registries. The survival of women with births will be compared to that of the comparison group us Cox Proportional Hazards Regression analysis, a technique that will allow us to control more completely for other factors related to survival, including nodal status, treatment, and estrogen receptor status, in evaluating relative survival after childbirth.

## **II. BODY**

describe experimental methods and results obtained relative to goals of research

### ***A. Experimental methods used***

To achieve our objective, we are using a retrospective cohort design, comparing the survival of young women who give birth after a diagnosis of breast cancer with that of a matched comparison group of breast cancer patients who do not give birth. Emphasis will be placed on determining the disease status of women at the time the pregnancy occurred (one calendar year prior to the birth, or the "reference date") in an attempt to ensure that the health status of the women with and without births are similar. Young women less than 45 years of age with breast cancer diagnosed during 1980-1990 from three population-based cancer registries (Seattle, Los Angeles, Detroit) have been identified. This cohort file is being linked with birth certificate records for 1980-1993 in each state to identify women who have a live birth after their diagnosis of primary breast cancer. Subjects eligible for inclusion in the comparison group will be selected from among women without births at each site who are known to be alive at the reference date, and will be matched on age, stage at diagnosis, and year of diagnosis. All women will be followed up using routine methods to determine their survival after reference date through 1995 (follow-up ranging from 5 to 15 years, with an expected mean follow-up of approximately 7.7 years).

After creation of the data sets containing registry and birth certificate information from each site, data will be consolidated into one research data set in Seattle, where data analysis will occur. Cox proportional hazards regression will be used to evaluate the relative survival after reference date of women with and without subsequent births. This method allows for adjustment in the analysis of potentially confounding variables obtained from registry data (tumor size, nodal status, estrogen receptor status).

## ***B. Results obtained relative to our stated goals***

Per our revised Statement of Work, our first year of operation has consisted to activities related to data acquisition and the refining of linkage protocols. The investigators from all Sites (Drs. Mueller, Deapen, and Simon) met in the Spring in Los Angeles to discuss linkage and matching issues, and to apprise each other of progress. Activities which occurred during the last year are described below in more detail:

*b1. Identification of young women with breast cancer at all sites* - At all three sites, women <age 45 diagnosed with breast cancer during the years 1980-1993 have been identified and preliminary data files containing pertinent identifying information have been prepared for linkage. This activity occurred within each cancer registry after appropriate Institutional Review Board Approvals had been obtained. In Seattle, 2,651 women who fit the preliminary inclusion criteria have been identified. In Detroit, 4496 women have been identified who meet study criteria.

*b2. Procurement of birth certificate data tapes* - Appropriate permission has been obtained by the investigator, and the co-investigators in other states, from all relevant state Departments of Health for use or purchase of birth certificate data files for 1990-93.

*b3. Development of linkage protocols* - Because of varying data file structures and institutional requirements, the linkage protocols differ slightly differently at each site. In Seattle, Dr. Mueller met separately with Dr. Michael Garrick, PhD., the IRB coordinator for the State of Washington and Dr. David Thomas, the CSS director to refine protocols for the birth certificate data acquisition and record linkage. A protocol was designed to meet the confidentiality requirements of both institutions which was subsequently approved by both relevant Institutional Review Boards. Resultant modifications in the previously approved protocols do not alter the substance of the protocol, but they do designate where data transactions occur and specify who may have access to confidential information from both data sources. Data linkage is occurring using this protocol at the Fred Hutchinson Cancer Research Center. The details of this protocol were passed on to the other two study sites as a model system should similar requirements arise.

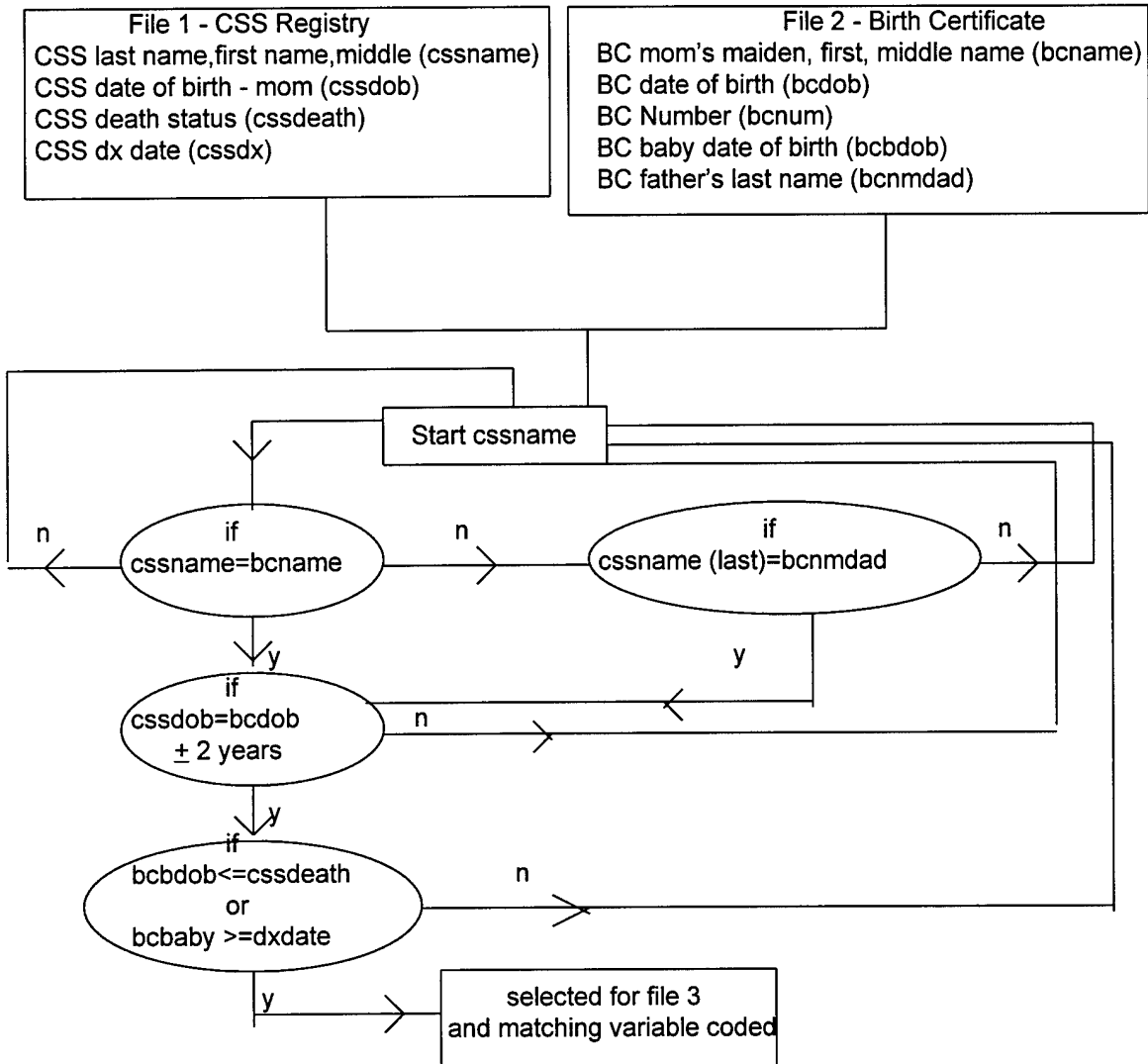
In Los Angeles, Dr. Deapen's communications with the Department of Health have ascertained their approval for the data linkage, which will occur at the University of Southern California. Dr. Simon has had similar communications with the Michigan Department of Health however, because of current interagency agreements between the Cancer Registry in that area and the Health Department, data from the registry routinely goes to the Health Department and thus, the records linkage will occur there. Detroit will run their data linkage programs in two stages due to historical format changes present in the birth certificate tapes. The first stage will be run on the data for the years 1989 to 1993. The researchers in Detroit have developed a linkage program in conjunction with the Department of Health that will be run at the Department of Health to identify the exposed women from 1989 to 1994. The second stage will be run on the data from the

years 1980 to 1988 and a protocol for that stage of matching is being developed. Records linkage for a portion of the Michigan data will begin shortly.

*b4. Development of linkage program* - A model linkage program using the SAS programming language has been developed and is being used by the project programmer, Kay Byron, at the Cancer Center in Seattle. She has been working with the State Vital Records Data Coordinator, Mr. Bill O'Brien, in the development and piloting of a linkage program for the data files. Per our initial strategy, linkage of files is currently underway in Seattle, and our programming and logic are being forwarded to the other sites for their use and review. A description of the programming rationale and a flowchart follows.

Initially, the data linkage of registry and birth certificate data is based on mother's first name, birth surname, birth date, father's last name, provided in the birth certificate file, with name and birthdate in the cancer registry file. Within the program, women from the registry are classified as being definitely linked, possibly linked, and unlinked. Women falling in the second category, those possibly linked, will be evaluated individually and reclassified by the investigators at each site following review of registry and birth certificate records. Linkage consists of a five step process as outlined below. This process is designed to assure those involved outside the CSS are blinded to the cancer cases.

Flow Chart of Breast Cancer and Childbearing Study Linkage Program between the FHCRC and the UW. Run for every year between 1980-1993:



The program will tally the amount of potential links and then randomly select three times the number of birth certificate numbers. Total number of birth certificates in file= 3 \*N of links  
The end result of this program is 2 files (file 3)

1) FHCRC - Kay Byron's file includes

Birth Certificate # CSS # name matching variable
---

2). UW - Bill O'Brien's file includes

Birth Certificate # Birth Year
-----------------------------------

At UW, Bill O'Brien runs a program to get the rest of the birth certificate information on those birth certificate numbers from his file. The result is file 4. He gives Kay Byron at the FHCRC file 4. Kay Byron merges her file 3 to file 4. If any CSS numbers are blank and the matching variable code is appropriate for no match, they are deleted. The resulting file, file 5 is verified and edited for accuracy of the possible links. The result from this program from the years 1988-1993 from the Seattle data follows.

The results of the preliminary linkage of Seattle area data and birth certificates for Washington, for the years for which linkage has occurred to date, are shown below. Possible linkages within the program allow for the a name or address change, or the possibility an error in entry of a birth date and thus, are likley to overestimate the number of true linkages. However, they will be further refined by inspection of relevant documents and the numbers of cases potentially linking is similar to that predicted by previous preliminary linkage procedures.

Number of Potential links between Seattle area Cancer Registry data and the Washington State Birth Certificate Tapes.

Birth Year	Number of Potential Links
1987	86
1988	94
1989	103
1990	103
1991	74
1992	76
1993	53

*b5. Data management related to selection of comparison cohort without births* - For each breast cancer case found to have had a subsequent live birth, five women, matched on certain characteristics, will be selected as candidates for the comparison group from among women without births after diagnosis. To ensure that the health status of each woman in the comparison groups as similar as possible to that of her matched woman who gave birth, a "reference date" will be established, consisting of the calendar year prior to the year in which the birth occurred after diagnosis. Comparison candidates will be selected from among women who are known to be alive at that reference date, and will be matched on age, year of diagnosis, and disease stage at diagnosis. Since the registries routinely link with death certificates, women who are identified by the registry as deceased prior to reference date can be excluded from the comparison group.

In order to conduct this activity, careful data management will be necessary. In Seattle, we have developed a data tracking system that will be kept on the Hewlett Packard mainframe computer at the FHCRC, which also houses the CSS data. This tracking system will allow the "exposed" data to be linked with other CSS data from which to build the comparison group. This data tracking system will be utilized when the exposed women are identified by the method described above. The variables in this tracking system includes: name, address, vital status, CSS identification number, a case/control identifying variable, a study id which identifies site and comparison matches (for use when the data from all three sites is merged), diagnosis date, reference year, date

of birth, disease stage and recurrence status, and variables that identify child's birth date, birth certificate number, and the quality of match code (definite link, possible link, or no link). The birth match variables allows for the possibility of more than one birth. Although computer specifications for tracking vary at each site, the details of this system will be made available to the other two study sites so that similar care will occur in the selection of the unexposed comparison subjects.

### **III. CONCLUSIONS**

#### **A. Implications of work completed to date and description of changes made to procedures**

Per our statement of work, things are progressing as anticipated. Considerable preliminary groundwork was required in order to obtain approvals for data use and to obtain the necessary tapes. The investigators have held one meeting and have been in frequent phone, FAX, and/or email communication and study managers and support personnel have been identified. A Study Coordinator, Janet Kelly, has been hired in Seattle to coordinate efforts at all sites.

Several meetings or communications between the investigators and relevant Registry and Health Department personnel have also taken place. Appropriate protocols between Cancer Registries and Health Departments have been developed, or are in progress and data linkage is occurring in the study core site, Seattle. Changes that occurred related to the linkage protocol in Seattle addressed the location of the operation (data linkage will occur at the Cancer Center) and specification of who may have access to identifying information (the Cancer Center investigator, and staff) and did not change the outcome of the process. The number of exposed women identified in preliminary linkages in Seattle is consistent with that anticipated based on the pilot data. Our efforts in the next study period will include customizing our linkage and review procedures in Seattle for use at the other sites.

Once the exposed cohort is identified, the comparison group will be built. In the spring meeting of the investigators, issues of selection and matching criteria for this comparison group were addressed. Specifically discussed was that if an exact match on age and disease stage cannot be found for an exposed women in the upper ranges of age, the matching age window should not be  $\pm$  two years as originally planned. This is because as a otherwise healthy women ages, her fertility naturally decreases. To include a women without a pregnancy in the upper ranges of age in the comparison group could possibly bias the comparison group into having a longer fertility age range. To remedy this, the investigators decided that if an exact match could not be found for an exposed women in the upper ranges of age, than a younger women alive and free of disease recurrence - two years of the reference date would suffice.

Also raised was the possibility that exactly matching women for the comparison group for every exposed women may not be found. Possible ways to obtain a high ratio of matched comparison subjects by relaxing matching criteria were discussed, and a priority of criteria was established, as some might potentially impact the results more than others. Tentatively, pending our findings concerning the numbers of exactly matching subjects found at each site, it was suggested that linkages based on year of diagnosis might be first to be relaxed. Linkage based on race may be relaxed, but a white/non-white status comparison will be maintained. Linkages based on age at diagnosis, stage at diagnosis were felt to be most importantly maintained. No relaxation of the criteria that comparison women survive until reference date will occur. During the next study period, these issues will be dealt with more specifically as the nature of our data structure emerges. The investigators will continue to communicate frequently, and will meet again during the next year to discuss the results of the data linkages and comparison group selections.

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